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REVIEWS

Cardiac Complications in Acquired Immunodeficiency Syndrome (AIDS): A Review

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Acquired immunodeficiency syndrome (AIDS) has become an increasingly important health problem worldwide. This review focuses on its cardiac complications. The key elements in the clinical syndrome are the opportunistic infections and the cancer that occur as a by-product of the immunodeficiency process. However, as early diagnosis, aggressive therapy and better supportive care become increasingly available, with consequently longer survival rates, cardiac lesions other than those due to opportunistic infections or malignancy should be seen.

Cardiac complications are described in terms of the pathologic lesions, the clinical manifestations that ensue as a result of the pathologic lesions and the cardiac abnormalities that can occur from administration of the various therapeutic agents in the syndrome.

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Progressive dysfunction of multiple organ systems occurs in acquired immunodeficiency syndrome (AIDS). The pulmonary, gastrointestinal and neurologic systems have been the principal targets, but it appears that the heart, too, should be part of the total involvement. The early necropsy studies failed to indicate the presence of cardiac lesions that had any degree of clinical significance. However, cardiac lesions currently being reported are quite diverse and reflect the various pathologic pathways of cardiac involvement in AIDS. Lesions other than those due to opportunistic infections or malignancy should be seen as early diagnosis, aggressive therapy and better supportive care become increasingly available and survival time lengthens. Moreover, the rapidly escalating prevalence of AIDS itself mandates awareness of cardiac involvement in this disease, since it is most likely that cardiac complications of AIDS will be encountered with increasing frequency. In this review, these complications will be described in terms of the pathologic lesions, the clinical manifestations that ensue as a result of the pathologic lesions and the cardiac abnormalities that can occur from administration of the various therapeutic agents used in the management of AIDS.

There have been several necropsy studies (1–5) describing the cardiac lesions in AIDS. The causes of death in these initial studies were ascribed to a variety of opportunistic infections and neoplasms. Survival time from initial diagnosis to death varied from 2 weeks to 22 months. The striking feature in these studies was the failure of the necropsy findings to indicate that the presence of the cardiac lesions had clinical significance. Hui et al. (1) were the first to point out the anomalous patterns of infection at postmortem examination, such as cytomegalovirus infection without evidence of inflammation and acid-fast infection without granuloma formation. The various cardiac lesions that have been described in AIDS are listed in Table 1.

Myocarditis

Clinical manifestations of myocarditis are dependent on the severity of the inflammatory process and, if focal in type, on the location of the lesion. For example, James et al. (6) described the occurrence of conduction disturbances when focal lesions involve the His bundle or its branches. Clinical manifestations may be completely nonexistent, obscured by the systemic manifestations of the underlying syndrome or strikingly severe with full-blown congestive heart failure or disabling arrhythmias, or both (7).

The complete etiologic spectrum of myocarditis in AIDS has not, as yet, been completely delineated. There appear to be many etiologic factors acting separately or in combination. An infectious factor due to opportunistic infection is certainly well documented.

Opportunistic infections. The list of opportunistic infectious agents (Table 1) that have been identified in AIDS-

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Table 1. Cardiac Lesions in AIDS

Myocarditis
Opportunistic infections
Pneumocystis carinii
Mycobacterium tuberculosis
Mycobacterium avium-intracellulare
Cryptococcus neoformans
Aspergillus fumigatus
Candida albicans
Histoplasma capsulatum
Coccidioides immitis
Toxoplasma gondii
Herpes simplex
Viral agents
Cytomegalovirus
Human immunodeficiency virus (HIV)
Lymphocytic myocarditis
Noninflammatory myocardial necrosis
Microvascular spasm?
Endocarditis
Marantic endocarditis (nonbacterial thrombotic endocarditis)
Healed bacterial endocarditis
Aspergillus endocarditis
Pericarditis
Infectious
Tuberculous
Herpes simplex
Noninfectious
Pericardial effusion
Cardiomegaly
Right ventricular hypertrophy or dilation
Biventricular dilation (congestive cardiomyopathy)
Vascular lesions
Arteriopathy
Myocardial infarction
Malignancy
Kaposi's sarcoma
Malignant lymphoma
Toxic lesions
Drug-induced
Drugs used in combating opportunistic infections
Anti-HIV drugs

associated myocarditis is by no means complete, since further studies will almost surely identify other agents. However, despite the broad range of infectious agents to which patients with AIDS are potentially and theoretically susceptible, most of the studies incriminate a relatively uniform and characteristic pattern of such agents (8) (Table 2). Multiple infections in combination are also frequent (9,10). Although current therapy has prolonged survival, its primary impact on the infectious aspect of AIDS (that is, regarding the opportunistic agents) has been to shift the type of infections from the potentially treatable to the untreatable category. This shift will have some bearing on the ultimate outcome of AIDS-associated myocarditis due to such infectious agents.

Among the various opportunistic infectious agents, some have come under more careful scrutiny. Examples of these are *Toxoplasma gondii, Mycobacterium tuberculosis*, cryptococcal myocarditis and cytomegalovirus infection. Lewis et al. (11) reported on two patients with acute myocarditis due to *Cryptococcus neoformans*. Although these patients had widespread cryptococcal infection, neither had clinical evidence of heart disease.

Toxoplasma gondii *was isolated from mice infected with cardiac tissue from one patient (12).* This same patient's cardiac tissue showed nonspecific wavy changes in the myocardial fibers, but no *Toxoplasma* cysts were identified on histologic section. *Toxoplasma* myocarditis could represent a reactivation of toxoplasmosis as a result of the deficient immune response in AIDS rather than a new opportunistic infection (12). Although this is a difficult question to resolve, the answer really does not matter from a purely therapeutic point of view, since management of the infection itself is not altered.

One would expect Mycobacterium tuberculosis *to be a very common agent* because, in the presence of defective cell-mediated immune systems, tuberculous lesions can disseminate widely. However, tuberculosis has not been a conspicuous feature of AIDS except in Haitians, in whom this disease is frequent to begin with (13). Pitchenik et al. (14) reported a high (50%) incidence of tuberculosis in their survey of 20 heterosexual Haitian residents in Miami. However, even though myocarditis with tuberculous involvement has been described, it is not usual among the present studies. More usual is the occurrence of pericardial tuberculosis as part of a widely disseminated process.

Role of viral agents. The role of viral agents, such as cytomegalovirus as well as human immunodeficiency virus itself, should also be seriously considered. Human immunodeficiency virus was isolated in culture from an endomyocardial biopsy specimen from a patient with AIDS with congestive cardiomyopathy (15). Myocardial involvement in cytomegalovirus infection has been previously reported (16), but is rarely seen in immunosuppressed patients. Although cytomegalovirus infection has been reported as a common histologic finding in patients with AIDS, the typical owl's eye inclusion bodies have only rarely been found within the myocardium itself (1,17–22). Because it is well known that cytomegalovirus infections can cause tissue necrosis without associated inflammatory changes, it is still possible that cytomegalovirus or other viruses, including human immunodeficiency virus, were the responsible agents in those necropsy studies of patients with AIDS in whom myocardial necrosis without inflammation was seen (21,22).

Human immunodeficiency virus may damage the monocytes either by direct infection with ultimate cytolysis or by "innocent bystander destruction," as proposed by Ho et al. (20) in their explanation for the presence of neuroglial cell damage in AIDS-associated subacute encephalitis. In

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Table 2. Infections in AIDS

Microorganisms	Common Locations	Common Clinical Manifestations
Protozoa		
Pneumocystis carinii	Lungs	*Pneumocystis* pneumonia
Toxoplasma gondii	CNS, eyes, heart	CNS mass; chorioretinitis
Cryptosporidium species	GI tract	Diarrhea
Entamoeba histolytica	GI tract	Diarrhea
Isospora belli	GI tract	Diarrhea
Giardia lamblia	GI tract	Diarrhea
Fungi		
Candida species	Oropharynx, esophagus, bladder, lungs	Thrush, esophagitis, cystitis, pneumonia
Cryptococcus neoformans	CNS, lungs, lymph nodes, bone marrow, blood, urine	Meningitis, pneumonia, dissemination
Histoplasma capsulatum	Lymph nodes, bone marrow, lungs	Dissemination
Coccidioides immitis	Lungs, lymph nodes, skin	Dissemination
Bacteria		
Mycobacterium avium intracellulare	Lymph nodes, bone marrow, lungs, skin, blood, spleen, liver	Lymphadenitis, pancytopenia, pneumonia, dissemination
Mycobacterium tuberculosis	Same	Same
Nocardia asteroides	Lungs	Pneumonia
Viruses		
Cytomegalovirus	Disseminated (lungs, adrenals, eyes, CNS, liver, kidneys, intestinal tract, lymph nodes, blood); predilection for endothelial cells	Pneumonia, chorioretinitis, encephalitis, hepatitis, esophagitis, intestinal tract, enteritis, colitis, adrenal insufficiency
Herpes simplex viruses	Mucocutaneous	Ulcerative mucocutaneous lesions
Epstein-Barr virus	Uncertain	Uncertain, Epstein-Barr–positive Burkitt's lymphoma
Polyoma viruses	CNS	Progressive multifocal leukencephalopathy
Poxvirus	Mucocutaneous	*Molluscum contagiosum*

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this mechanism, as the human immunodeficiency virus replicates itself within interstitial lymphocytes and macrophages, certain enzymes are released that are toxic to the monocytes. The application of nucleic acid probes for human immunodeficiency virus, cytomegalovirus and other opportunistic viral agents may help clarify the role of viruses in AIDS-associated myocarditis.

Lymphocytic myocarditis. In a retrospective study of 71 patients who died from AIDS, Anderson et al. (23) concluded that myocarditis is a frequent finding at autopsy. At least 37 cases of myocarditis were found in their series. In the majority of these patients, however, the etiology remained idiopathic. However, in seven cases, viral, protozoan, bacterial, fungal and myocardial opportunistic pathogens were present. The myocarditis in their series was described as being usually focal and mild, with a mononuclear infiltrate. The mild degree of inflammatory response seen in their series could possibly be the result of the marked cell-mediated immune deficiency in AIDS.

Roldan et al. (24) reported a similar high incidence of myocarditis. Two histologic patterns were seen: 1) a lymphocytic infiltrate with necrosis of the myocardial fibers, and 2) a lymphocytic infiltration without myocardial fiber necrosis. In six patients with both lymphocytic infiltration and necrosis of the myocardial fibers, tachyzoites of *Toxoplasma gondii* were seen within these foci. No specific etiologic agent could be found in the remaining cases.

A distinction must be made between the histologic findings of AIDS-associated myocarditis versus secondary myocarditis due to known pathogens as well as idiopathic myocarditis. In AIDS-associated myocarditis, the histologic findings most frequently described to date have been nonspecific inflammatory infiltrates without myocyte damage that, therefore, do not meet the so-called Dallas criteria (25). Both an inflammatory infiltrate and myocyte damage or necrosis are required for the histologic diagnosis of myocarditis according to these criteria (25). The significance of this distinction in regard to the more prevalent histologic picture of AIDS-associated myocarditis has yet to be defined.

Noninflammatory myocardial necrosis. Two explanations can be offered for the presence of myocardial necrosis without inflammation in those cases of AIDS that present this histologic pattern. One is that necrosis of the myocytes can be brought about by virtue of the long-term stress that patients with AIDS are subjected to as a result of the tragic implications of their disease; the pathway being mediated

through prolonged and excessive secretion of catecholamines (26). The other explanation is that because cytomegalovirus infections can cause necrosis without inflammation, it is possible that cytomegalovirus or other viral agents, including human immunodeficiency virus, are the precipitating cause of the myocardial necrosis.

A catecholamine-induced myocarditis is a distinct possibility through repeated transient focal or widespread ischemia as a result of episodes of microvascular spasm (27). Factor and Sonnenblick (28) advance this sequence as an important pathogenic mechanism in the development of certain types of congestive cardiomyopathy. It is not too unreasonable then to conjecture that this mechanism could also prevail in AIDS-induced myocarditis as an aggravating rather than as a sole etiologic factor.

Endocarditis

Marantic endocarditis. The most common endocardial lesion seen in the studies to date is nonbacterial thrombotic bacterial endocarditis—so-called Marantic endocarditis (17,19,29). Any of the valves can be involved. Nonbacterial thrombotic endocarditis is known to be associated with long-term wasting illnesses and malignancies (30), and this may be the reason for finding it in AIDS.

Marantic endocarditis was associated with disseminated intravascular coagulation in one patient and systemic embolization in others (17,19). In the series of Cammarosano and Lewis (17), systemic embolization with cerebral infarcts occurred in the patient with the vegetations involving the mitral valve, and in another with vegetations involving all four valves. All the vegetations were friable. Microscopically, they consisted of a fribin mesh with few chronic inflammatory cells. Neurologic complications in AIDS have been reported, and it is possible that embolization was one factor in these complications in some of the patients described by Snyder et al. (31).

Healed bacterial endocarditis. This lesion has also been reported, but it probably represents antecedent infection rather than an AIDS-associated condition because bacterial endocarditis has been reported in those patients with a history of intravenous drug abuse.

***Aspergillus* endocarditis.** One case of *Aspergillus* endocarditis was reported in an individual with concomitant pulmonary aspergillosis (32). In this patient, a two-dimensional echocardiogram showed a large vegetation on the anterior mitral leaflet, and necropsy revealed scattered myocardial abscesses containing *Aspergillus fumigatus*, with one large abscess located just beneath the posterior mitral leaflet. This was probably the origin of the septic embolus that caused the sudden onset of left hemiparesis and aphasia in this individual. At no time did this patient have a cardiac murmur, positive blood culture for *Aspergillus fumigatus* or clinical evidence of cardiac dysfunction.

Pericarditis

To date, all the patients with pericardial disease have had concomitant involvement of the myocardium. The pericarditis was usually nonspecific in origin, associated with Kaposi's sarcoma or due to a pathogen such as *Mycobacterium tuberculosis* and *Cryptococcus* (24,33). Many times, pericardial involvement has been noted clinically by the occurrence of pericardial effusion (24,33). Echocardiographic evaluation has proved to be an excellent diagnostic tool in detecting pericardial effusion and especially in confirming the presence of cardiac tamponade (2). This is important to realize, since the clinical picture of AIDS may be so overwhelmingly dominated by the impact of the opportunistic infections that cardiac dysfunction may be easily obscured or unrecognized.

Pericardiocentesis may yield a clear-appearing serosanguineous fluid (2). In many instances, cultures of the pericardial fluid of bacteria or fungi have yielded no growth. The first case of tuberculous pericarditis was reported by D'Cruz et al. (33). The patient had disseminated tuberculosis with miliary tubercles in many organs. Both layers of the pericardium were studded with various sized tuberculous granulomas. Grossly, there was mild dilation and flabbiness of all the cardiac chambers, with no evidence of hypertrophy. The microscopic appearance of the myocardium was characterized by a moderate, diffuse, nonspecific interstitial infiltrate of neutrophils and lymphocytes. There was also a patchy dropout of myocardial fibers. During life, pericardiocentesis confirmed the echocardiographic diagnosis of pericardial effusion. Diffuse left ventricular hypokinesia was also demonstrated with echocardiography in this patient.

Cardiomegaly

Cardiomegaly reported at necropsy has consisted of right ventricular hypertrophy or dilation, biventricular dilation or four chamber enlargement.

Right ventricular hypertrophy. The cause of right ventricular hypertrophy can no doubt be ascribed to the pressure overload imposed on the right ventricle as a result of pulmonary hypertension. Severe or repeated pulmonary infections that occur so commonly in AIDS can certainly give rise to either acute or chronic pulmonary hypertension. The pathophysiologic mechanisms for this are well known.

Congestive cardiomyopathy. Biventricular or four chamber dilation is the characteristic postmortem finding in dilated congestive cardiomyopathy. In the series of Anderson et al. (23), myocarditis was present in all cases of AIDS-related deaths with gross evidence of biventricular dilation. Myocarditis was not seen in those cases showing only right ventricular dilation, pericardial effusion or cardiac malignancy (24).

There is considerable evidence in support of the concept

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that the syndrome of dilated cardiomyopathy is, at times, a postviral disorder (34). This evidence includes the findings on endomyocardial biopsy of an inflammatory infiltrate in some patients with the clinical features of dilated cardiomyopathy (35,36). Other evidence pointing to a viral origin has been the detection of high viral antibody titers (37), viral-specific ribonucleic acid (RNA) sequences (37) and apparent viral particles. Moreover, several important studies (38–40) have highlighted abnormalities of T cells, especially the suppressor T cells, in some cases of dilated cardiomyopathy.

The presence of a lymphocytic infiltrate in the myocardium of patients with dilated cardiomyopathy may be advanced as an indication of the presence of active myocarditis but, as Tazelaar and Billingham (41) have reported, this is not necessarily so. Their findings could be construed as being the link, albeit weak, in the argument that attempts to extrapolate the preceding constellation of evidence into documentation of the thesis that human immunodeficiency virus itself cannot only induce a myocarditis, but that this inflammatory process could result in dilated cardiomyopathy.

Although one case alone does not provide adequate foundation for a pathogenic mechanism, the isolation of human immunodeficiency virus by culture from an endomyocardial biopsy specimen in an AIDS-associated congestive cardiomyopathy lends support to the probability that such a mechanism can exist (15). In addition to infectious agents, viral or otherwise, dilated cardiomyopathy can be caused by cardiotoxins, hypersensitivity reactions and certain dietary deficiencies (34).

Drug-induced cardiomyopathy does not appear to be a particularly important factor, and is discussed elsewhere. Vitamin deficiency, especially of vitamin B_1, is certainly a possibility in these severely ill patients. However, although vitamin B_1 deficiency might play a role in AIDS-associated dilated cardiomyopathy, the probability is that it is a secondary factor, the most likely possibility being that the cardiomyopathy is secondary to myocarditis and viral in origin (34). As mentioned before, there is much documented evidence of myocarditis due to any number of viruses, including the Epstein-Barr virus and cytomegalovirus (42,43). Immune suppression, as in AIDS, may very well increase the likelihood of infection with these known cardiotropic viruses. With regard to human immunodeficiency virus itself, more work needs to be done concerning its role in the development of an initial myocarditis with the consequent emergence of dilated cardiomyopathy.

The postmortem gross findings of dilated cardiomyopathy in patients with AIDS have included increased heart weight, with either biventricular or four chamber dilation and a pale-appearing myocardium (24,44). Microscopically, these cases have shown evidence of both hypertrophy in focal areas, and focal areas of atrophy with diffuse loss of the myofibrillar elements and vacuolization of the atrophic myocytes (24,44). Focal areas of inflammatory infiltrate have been seen containing lymphocytes, histiocytes and necrotic myocytes. Electron microscopic studies have revealed loss of myofibrils, lipid deposition and an increase in mitochondria. In the study of Cohen et al. (44), no viral inclusion bodies were noted and heart tissue homogenates inoculated into neonatal mice intracerebrally, intraperitoneally and subcutaneously showed no evidence of viral pathogens. This same group also cultured heart tissue on human foreskin fibroblasts, WI-38 cells and Hep-2 cells with negative results.

The clinical manifestations of AIDS-associated dilated cardiomyopathy are similar to those of dilated cardiomyopathy of any cause. There is, of course, the clinical spectrum of congestive heart failure with radiographic evidence of cardiomegaly. The echocardiogram is most useful in detecting global hypokinesia with decreased fractional shortening, decreased ejection fraction and dilation of the various cardiac chambers with abnormal left ventricular end-diastolic and end-systolic dimensions (2,3). On auscultation, nonspecific abnormalities such as systolic ejection murmurs, gallop rhythm and arrhythmias may be present. The electrocardiogram (ECG) is also nonspecific, demonstrating a pattern of left ventricular hypertrophy or strain and nonspecific ST-T changes.

Dilated cardiomyopathy has been described in children with congenital AIDS (45). In these children, the clinical manifestations have included the various stigmata of congestive heart failure, roentgenologic evidence of cardiomegaly, ECG changes consisting of T wave abnormalities and voltage criteria of left ventricular hypertrophy and echocardiographic evidence initially of left atrial and left ventricular dilation with decreased fractional shortening in association with poor septal and posterior wall motion. Over the course of 2 years, these abnormalities are followed by evidence of increasing right atrial and right ventricular enlargement, as well as tricuspid valve thickening and nodularity. Steinherz et al. (25) also cite the development of right axis deviation on the ECG in those individuals with evidence of right ventricular hypertrophy, and advance the probability that these are indications of pulmonary hypertension due to repeated pulmonary infections (45). In the series of Joshi et al. (46), those children who manifested cardiovascular dysfunction during the course of their illness presented the following signs and symptoms: shortness of breath, easy fatigability, tachypnea, sinus tachycardia with gallop rhythm, scattered rales, hepatomegaly, and radiographic evidence of cardiomegaly.

Vascular Lesions

Several types of vascular lesions have been described in AIDS. These are an arteriopathy, with or without aneurysmal formation, a fibrocalcific lesion, endothelial proliferation

in association with Kaposi's sarcoma and thrombotic episodes of the coronary artery tree (47).

Arteriopathy. Joshi et al. (47) reported the occurrence of arteriopathy in children with AIDS. In six children who died with AIDS, two types of arteriopathy were detected: inflammatory and fibrocalcific. The inflammatory lesion consisted of a vasculitis or perivasculitis in the brain in those children who had clinical manifestations of AIDS-associated encephalopathy. The fibrocalcific lesions were described as intimal fibrosis with fragmentation of elastic tissue and fibrosis and calcification of the media with variable luminal narrowing. The fibrocalcific arteriopathy was seen in various organs, including the heart, and involved mostly the small- and medium-sized arteries. In one case, aneurysms of the right coronary artery were seen in association with intraluminal thrombosis and myocardial infarction. Death in this instance was attributed to myocardial infarction.

Perivasculitis of the retina demonstrated by ophthalmoscopic examination has been described (48) in both children and adults with AIDS. This condition may have the same pathogenesis as the inflammatory arterial lesions in the myocardium of the patients described by Joshi et al. (47).

Aneurysm. The three aneurysms that have been described (47) involve a 3 cm segment of the proximal portion of the right coronary artery. The aneurysms were fusiform and varied in size from 0.6 to 0.8 cm in diameter. All contained recent thrombus, and their walls had multiple areas of calcification, as well as fragmentation of the elastic tissue with fibrosis of the intima and media. The left coronary artery had similar fibrocalcific lesions of lesser severity and without aneurysmal formation. None of the coronary arteries showed any evidence of inflammation or necrosis of their walls.

Fibrocalcific arteriopathy. The fibrocalcific arteriopathy described to date (47,49–51) appears to be distinctive and separate from Kawasaki's disease and idiopathic arterial calcification of infancy. This conclusion was primarily based on clinicopathologic and immunologic features. The pathogenesis of fibrocalcific arteriopathy, however, has yet to be delineated. The most obvious etiologic factor would appear to be the human immunodeficiency virus itself, but there are no studies to prove this. It is also possible that the immunodeficient state may be responsible because of the persistent and unchallenged antigenic stimulation (47). Because elastic tissue degeneration and fragmentation are the initial steps before fibrosis and calcification occur, there also may be a relation to both endogenous and exogenous elastases (52). The children studied live up to 40.5 months. The longer survival time in these patients may have been sufficient to allow development of vascular lesions, so that there is a distinct possibility that the arteriopathy described may be seen in the future with increasing frequency as longer survival rates are obtained.

Malignancy

Homosexual individuals show a higher incidence of the following types of malignancies: Kaposi's sarcoma (cutaneous, mucocutaneous, lymph nodes, gastrointestinal tract, lung and liver), high grade lymphoma (central nervous system, liver and disseminated) (53–57), oropharyngeal squamous cancer (58) and cloacogenic carcinoma of the rectum (59). The incidence of neoplasia in AIDS has been reported to be 39%. Kaposi's sarcoma is the most common neoplasm seen (60–62).

Two types of malignancies affecting the heart have been described in AIDS. These are Kaposi's sarcoma and malignant lymphoma (4,5,8,63,64). Again Kaposi's sarcoma is by far the most common.

Kaposi's sarcoma. This is a tumor that is said to arise from endothelial tissue. Although involvement of the heart in AIDS-associated Kaposi's sarcoma is usually part of a widely disseminated process, primary Kaposi's sarcoma of the heart has also been described (63). Nodular sarcomatous lesions involving the entire anterior cardiac wall were found at necropsy, with the patient manifesting clinically a nonspecific cardiomegaly on X-ray study, along with sinus tachycardia and gallop rhythm. Death in this case was attributed to "febrile cardiogenic shock." Primary cardiac Kaposi's sarcoma has also been reported in individuals without AIDS (63) but, because of the high incidence of Kaposi's sarcoma in AIDS, the occurrence of the sarcoma in this case is probably more than coincidental.

In the series of Silver et al. (5), at necropsy, 28% (5 of 18 patients) had cardiac involvement with Kaposi's sarcoma as part of a widely disseminated process. In each of the five patients, Kaposi's sarcoma was found in the subepicardial fatty tissue. There was involvement of the adventitia of the ascending aorta in three, and of the pulmonary trunk in one. There was no narrowing of a coronary artery by external compression from the tumor. The survival time in these patients ranged from 6 to 22 months, and none had clinical manifestations of cardiac dysfunction as delineated by the clinical course, ECG changes and chest X-ray film.

Apparently, the epicardium is a common location for Kaposi's sarcoma because epicardial involvement has been reported by several investigators (4,8,17). In the series of Cammarosano and Lewis (17), the sarcomatous lesions were metastatic and were found on the epicardial surface with or without involvement of the underlying myocardium or overlying pericardium. In their one patient with myocardial invasion, the sarcoma had infiltrated a small branch of the left anterior descending coronary artery. Extensive myocardial involvement was also seen (17). Again, in all of these reports of sarcomatous involvement of the heart, there was a paucity of clinical cardiac dysfunction. As Fink et al. (2) have stated, the clinical cardiac findings in AIDS are "unobtrusive" and need to be searched for.

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Malignant lymphoma. Malignant lymphomas in AIDS are usually high grade with Burkitt-like cells (small and noncleaved) or large cell immunoblastic plasmacytoid types (64,65). In the majority of cases, they appear to originate from B cells, with most of them displaying a monoclonal pattern of immunoglobulin staining. In some cases, the Epstein-Barr virus genome has been demonstrated in the proliferating cells (65).

In normal individuals, cell-mediated immune mechanisms are quite efficient in eliminating Epstein-Barr virus-transformed B lymphocytes (66). The immunodeficient patient, be it in AIDS or otherwise, is unable to check the continuous proliferation of these transformed B lymphocytes. The process can be initiated from multiple clones, and in the continuing development of the lymphoma, one of the clones could assume a dominant advantage so that a monoclonal pattern of the proliferating B lymphocytes could emerge (65,66).

Could there be a common thread in the causation of lymphomas in all immunodeficient syndromes? Several theories have been advanced in this regard. These include chronic antigenic stimulation, impaired immunosurveillance, reactivation of latent oncogenic herpes-group viruses and, perhaps, direct oncogenic effects of immunosuppressant drugs (67–71). The direct oncogenic effect of immunosuppressant drugs, however, does not apply to AIDS, but all the other theoretical possibilities are worthy of further investigation.

The increased incidence of lymphomatous neoplasm in immune deficiency states first became noticeable after the increased usage of organ transplants (68). As time went on, the relation between non-Hodgkin's lymphoma and AIDS became increasingly evident (69,71). Extranodal sites of lymphoma are common in patients with AIDS, and metastatic involvement of the heart can occur as part of this disseminated process (5,55,70–73).

Primary lymphoma in the heart is extremely rare. It was found in only 5.6% in the Armed Forces Institute of Pathology series of 125 primary malignant tumors of the heart (73). Metastatic lymphoma, on the other hand, is much more frequent (73). There are two reports (74,75) describing the occurrence of primary cardiac lymphoma in AIDS.

Pathology. Whether primary or secondary, lymphomas involving the heart in AIDS are characterized by one of two different pathologic patterns. One consists of a diffuse infiltration that imparts a large pale appearance to the heart. The other pattern involves the epicardium, myocardium and endocardium in the form of focal circumscribed nodules (73–75). In the two cases of primary cardiac lymphoma reported by Guarner et al. (67) there were focal circumscribed lesions. Constantino et al. (74) observed that the heart was enlarged and showed "multiple and well-circumscribed homogeneous white, fish-flesh infiltrates in the left posterior and lateral walls as well as in the interventricular septum." No valvulopathy or arteriopathic lesions were seen. Histologic sections of the myocardium contained patchy infiltrates of neoplasm composed of plasmacytoid lymphocytic cells that resembled the immunoblastic type of non-Hodgkin's lymphoma. There was also evidence of intense mitotic activity.

Clinical features. The clinical manifestations of lymphomatous involvement of the heart, whether associated with AIDS or not, may include cardiomegaly, pericardial effusion, congestive heart failure or progressive heart block (74–77). Sudden death is a rare event (76), and at least half of the patients have no clinical evidence of cardiac dysfunction. Gallium-67 and blood pool isotope studies can aid in the diagnosis (78). Tuberculous pericarditis appears as an area of uneven uptake surrounding an enlarged cardiac silhouette, whereas viral myocarditis or other inflammatory cardiomyopathies show not only a diffusely increased uptake, but also a prominent uptake localized within the left ventricle as a result of differences in left ventricular wall thickness (79). Echocardiography and ECG studies demonstrate nonspecific findings.

Toxic Lesions

There is adequate documentation that drugs can induce structural changes in the heart and blood vessels with resultant dysfunction (80). The morphologic changes in the heart could result in myocarditis, cardiomyopathy and endocardial fibrosis. The changes in the blood vessels can be expressed by an inflammatory process with or without necrosis, hyperplasia of the fibromuscular layer and thromboembolic phenomena.

The nonnecrotizing types of vasculitis are a manifestation of a delayed hypersensitivity reaction (81), whereas necrotizing drug-related vasculitis is more frequently related to a direct toxic effect. As yet, none of the drugs currently used in AIDS have been incriminated in this mechanism. In addition, none of the drugs currently utilized in AIDS-associated infections or malignancy have any relation to the development of endocardial fibrosis or vascular fibromuscular hyperplasia. On the other hand, mural thrombus formation is common in Adriamycin-related cardiomyopathy (82).

Drug-induced cardiomyopathy or myocarditis. This is an important aspect of the cardiac complications of AIDS. Because myocarditis due to hypersensitivity as well as the allergic type of vasculitis does not require an intact immune system, this mechanism could prevail in AIDS. In contrast, the remaining types of drug-induced morphologic changes that involve a mechanism independent of any immunologic mediation could occur in AIDS (Sweeney MJ, personal communication, 1988). In AIDS, T helper cell function is altered. Therefore, the ability to orchestrate immune function is hindered. This can result in uncontrolled hypergammaglobulinemia. If the immunoglobulin is of the IgE class,

then a type I hypersensitivity reaction could ensue, with myocarditis as an expression of this mechanism. Moreover, because the T suppressor cells are also capable of altering function, a state of hyperreactivity as well as "autoimmunity" could result with a high likelihood of expression. This type of immune abnormality could lead to reactions against self antigens and to chronic inflammatory-like diseases. It has already been demonstrated that human immunodeficiency virus-positive patients show high concentrations of immune complexes in their sera (Sweeney MJ, personal communication, 1988). This has the potential for causing not only local and systemic inflammatory lesions, but also disseminated intravascular coagulation and other abnormalities both in valvular tissue and in the blood vessels and major organs of the body.

A direct toxic effect is an important mechanism of drug-induced myocardial damage. This effect could be manifested as an acute or chronic myocarditis, either of which could ultimately result in cardiomyopathy. The preceding remarks merely emphasize the drug-induced cardiomyopathy or myocarditis can become an important aspect of the cardiac complications of AIDS and that this possibility should be kept in mind.

Categories of Toxic Drugs Used in AIDS

There are essentially two broad categories of drugs used in the management of AIDS: those that have as their objective the treatment of the opportunistic infections themselves or the malignancies that are seen in this syndrome, and those that are aimed at the elimination of the human immunodeficiency virus itself.

In addition, there are several important considerations in the treatment of AIDS-related opportunistic infections: 1) the immune deficiency state itself renders these patients less responsive to conventional therapy; 2) combinations of infections are often present; 3) prolonged and repeated therapeutic regimens are often necessary; and 4) there is a high incidence of drug-related toxic reactions in patients with AIDS.

Table 3 lists the pharmaceutical agents that have been or are currently being used in treating the various opportunistic infections and the etiologic agent against which the drug has been used.

Drug treatment of opportunistic infections. An important opportunistic infection in AIDS is caused by *Pneumocystis carinii.* In fact, *Pneumocystis carinii* pneumonia is the most common opportunistic infection in AIDS. It is usually treated with sulfamethoxazole-trimethoprim and pentamidine isethionate. The majority of AIDS patients treated for *P. carinii* pneumonia with sulfamethoxazole-trimethoprim will develop serious toxic reactions to the drug (83,84). However, adverse reactions in the heart have not been described to date, whereas when pentamidine isethionate was used, orthostatic hypertension was observed, especially when intravenous administration was at too rapid a rate (85,86).

There are two important drugs under investigation for the treatment of P. carinii *pneumonia* in those patients who cannot tolerate or do not respond to treatment with sulfamethoxazole-trimethoprim and pentamidine isethionate. These drugs are dapsone alone or in combination with sulfamethoxazole-trimethoprim and eflornithine (difluoromethylornithine). These two drugs do not cause a direct toxic effect on the myocardium, but it is conceivable that dapsone, because of the methemoglobinemia that can occur from its usage, can adversely affect the cardiovascular system by virtue of the resultant hypoxemia. Barbarash et al. (87) reported the development of a cardiac conduction disturbance during infusion with alpha-difluoromethylornithine (eflornithine). The conduction abnormality consists of first degree heart block and sinus bradycardia, progressing to complete heart block and finally electromechanical dissociation and death.

Amphotericin B is a highly toxic drug used in the very severe cases of infections with Cryptococcus neoformans, Aspergillus fumigatus, Histoplasmosis capsulatum, Coccidioides immitis and disseminated Candida albicans. Arrhythmia, ventricular fibrillation, hypotension, hypertension and cardiac arrest have been reported with amphotericin B. The drugs listed for the remaining etiologic agents in Table 3 have not been incriminated as having any adverse cardiac effects.

Chemotherapy. The role of chemotherapy in AIDS-associated Kaposi's sarcoma is purely palliative. As yet, there are no clinical data to suggest that this therapeutic modality will improve survival rates in these patients (88). Despite this guarded perception of its efficacy, chemotherapy, nevertheless, is currently being used in the management of AIDS-associated Kaposi's sarcoma, with the main drugs being the vinca alkaloids (vincristine sulfate and vinblastine sulfate). Doxorubicin (Adriamycin) in combination with vinblastine and bleomycin has also been used in AIDS-associated Kaposi's sarcoma. Myocarditis is a well documented complication of doxorubicin (89). Hypertension, unexpected myocardial infarction and cerebrovascular accidents have been reported with vinblastine.

Extensive data have been accumulated on the usage of alpha-interferon in AIDS-associated Kaposi's sarcoma. The adverse cardiovascular effects of this antiviral, antiproliferative and immunomodulatory agent are hypotension, hypertension and tachycardia (90–92).

Various protocols are under investigation at this time for the treatment of AIDS-related non-Hodgkin's lymphoma. The incidence of adverse cardiac effects in these protocols is, as yet, unknown, pending publication of the completed studies.

Treatment of immunodeficiency virus. The ideal therapeutic approach in the management of AIDS would appear

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Table 3. Opportunistic Infections in AIDS

Etiologic Agent	Pharmaceutical Agent	Cardiac Reactions
Pneumocystis carinii	Sulfamethoxazole-trimethoprim,	None reported
	pentamidine isethionate,	None reported
	dapsone,	Hypoxemia secondary to hemolysis and methemoglobinemia
	eflornithine (alpha-difluoromethylornithine)	Hypoxemia secondary to anemia from bone marrow depression
Cryptococcus neoformans	Amphotericin B,	Arrhythmia, ventricular fibrillation, hypotension hypertension, cardiac arrest
	flucytosine	None reported
Mycobacterium tuberculosis	Streptomycin,	None reported
	soniazide,	None reported
	nifampin	None reported
M. avium-intracellulare	No clearly active agent available	No clinical experience yet
Aspergillus fumigatus	Amphotericin B	As above
Histoplasma capsulatum	Amphotericin B	As above
Candida immitis	Amphotericin B	As above
C. albicans (disseminated)	Amphotericin B	As above
C. albicans (esophageal)	Retoconazole	None reported
C. albicans (oral)	Clotrimazole or	None reported
	nystatin or	None reported
	ketoconazole	None reported
Toxoplasma gondii	Sulfadiazine and pyrimethamine with leucovorin	None reported
Cytomegalovirus	DHPG (ganciclovir)	None reported
Herpes simplex and zoster	Acyclovir	None reported

DHPG = (1,3-dihydroxy-2-propoxymethyl) guanine.

to be the complete eradication of the human immunodeficiency virus. This approach is, of course, dependent on the unproved assumption that the natural and fatal progression of AIDS is a result of replication of the human immunodeficiency virus, beginning with the initial inoculum. Based on this assumption, two avenues of approach are currently under investigation. These include treatment with immunomodulating agents and antiviral therapy.

Foremost among the immunomodulator agents is interleukin 2 (88). This is a potent lymphokine that activates the effector agents of the immune response (B cells, cytotoxic T lymphocytes and natural killer cells). Future use of this agent is highly doubtful because of discouraging results so far. However, it is mentioned because it may be used in future clinical trials in combination with other agents and, perhaps, be responsible for adverse cardiovascular effects that are, as yet, unidentified.

A number of antiviral agents have been identified as being capable of inhibiting replication of human immunodeficiency virus in vitro. Most have in common the ability to inhibit the reverse transcriptase enzyme, which plays an important role in the life cycle of retroviruses. Azidothymidine (AZT), a nucleoside analogue, has emerged as the most promising of these agents. In a Phase 1 clinical trial, no adverse cardiovascular effects were noted. Richman et al. (93) also failed to note any adverse cardiac effects (93); their study, however, concentrated on the hematologic toxicity, and the study design, like that of Fischle et al. (94), failed to focus specifically on the heart. The incidence of drug-induced cardiac complications will most certainly change as newer agents are added to the therapeutic armamentarium.

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